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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/830,748	Applicant(s) KASHMIRI ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6,10-13,15,17,19,21-24,26,28,30,34,35,38,40-42 and 48-69* is/are pending in the application.

4a) Of the above claim(s) *42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,10-13,15,17,19,21-24,26,28,30,34,35,38,40,41 and 48-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11,13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-35, 38-41 in Paper No. 17 is acknowledged. The traversal is on the ground(s) that the subject matter of Group III (claim 42) drawn to a method of treatment should be classified in the same group as claims in Group I. This is not found persuasive because as stated in the restriction requirement the product is distinct from the method and in addition the product would be classified in 530/387.1 and the method in class 424/130.1. Clearly different searches and issues are involved in the examination of each group.

The requirement is still deemed proper and is therefore made FINAL.

2. Claim 42 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 17.

3. Claims 3, 5, 7-9, 14, 16, 18, 20, 25, 27, 29, 31-33, 36-37, 39, 43-47 have been canceled.

Claims 48-69 have been added.

Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34-35, 38, 40, 41, 42 have been amended.

4. Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34-35, 38, 40, 41, 48-69 are under examination.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10, 34-35, 53, 57, 58, and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 10, 53 and 57 are indefinite for reciting "three light chain hypervariable regions" and "three heavy chain hypervariable regions" because it is not clear if the phrase means only the CDRs or other residues including the frameworks.

b. Claims 34 and 35 are indefinite for reciting "wherein (1)...(2)...or (3)..." because it is not clear if both (1) and (2) have to be met and if so part)3) does not add any additional parts to the claim and in addition, then claim 35 is not further limiting if parts (1) and (2) must be met.

c. Claim 58 is indefinite because the residues recited in the claim are those that would be at positions in the 21/28'CL antibody.

d. Claim 69 is indefinite for reciting "instructions for using" because it is not clear what "use" is intended. Does the instruction tell how to make the antibody or how to use it for detection or treatment or some other "use"?

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 38, 40-41, 48-49, 51-55, 57-64, 66-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized antibody comprising CDR1 and 2 of the light chain from CDR 1 and 2 of LEN (SEQ ID NO:7 and 8) respectively and the other four CDRs from CC49 antibody (after completion of the deposit requirement see below) and said antibody further comprising at least one amino acid at positions 60, 61, 62, or 64 in the CDR H2 from the corresponding position in the 21/28'CL antibody or position 97 in CDR L3 is replaced with serine or position 94 is replaced with a threonine or both positions are replaced wherein the antibody binds TAG-72 and has reduced immunogenicity compared to a humanized CC49 antibody with a LEN framework and a 21/28'CL framework and a kit comprising such antibody and compositions comprising such, does not reasonably provide enablement for a humanized antibody wherein CDR1 and 2 of the light chain are from any antibody or from any CDR in the LEN antibody and the antibody has reduced immunogenecity compared to any humanized CC49 antibody and a kit comprising such or compositions comprising such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence

or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a humanized CC49 antibody wherein CDR1 and 2 of the light chain are either from any antibody (claim 11 for example) or from any CDR in the LEN antibody (claim 1 for example) and the antibody has reduced immunogenicity compared to any humanized antibody and kits and compositions comprising such.

The specification teaches antibodies that were humanized from a parent humanized CC49 antibody which has frameworks from LEN and 21/28'CL and the humanized antibodies have reduced immungenicity compared to the parent antibody and the antibody has CDR1 and 2 from the light chain from the corresponding CDRs in LEN, respectively, and CDR2 in the heavy chain comprises residues at positions 60, 61, 62, and 64 from the corresponding positions in the 21/28'CL antibody and a threonine at position 97 (see pages 28-46). The specification doe not enable a humanized antibody that binds TAG-72 and has lower immunogenicity that has CDR1 and 2 from the light chain from just any antibody or CDR1 and 2 from any CDRs in the LEN antibody.

The claims are not commensurate in scope with the enablement provided.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The

amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain CDRs from just any antibody or from any CDR from LEN, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

In addition, it would require undue experimentation to determine from all of the combinations of parental humanized antibody to start with in order to produce an antibody that would have reduced immunogenicity. There are literally a myriad of human frameworks that could be used to produce a humanized antibody and there are a myriad of ways to humanize an antibody by altering a myriad of residues. Thus, it

would require undue experimentation to know which parental antibody to compare the humanized antibody to in order to obtain an antibody that was less immunogenic.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

9. Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34-35, 38, 40-41, 48-69 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of the humanized CC49 antibody is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species of the humanized CC49 antibody. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

NOTE: A deposit requirement for the LEN or 21/28'CL antibodies are not required because the amino acid sequence of the variable domain of the antibodies is given in the specification (see page 5 and figure 11). The above rejection is made for the CC49 humanized antibody because the entire antibody is required because for immunogenicity the entire antibody which includes the hinge, CH1, CH2, and CH3 would be required and the amino acid sequence of these regions are not given in the specification.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-2, 4, 6, 10-13, 15, 17, 19, 21-24, 26, 28, 30, 34, 38, 40-41, 48-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mezes et al (U.S. Patent 6,495,137, filed 10/97) and further in view of Padlan et al (FASEB J. 9:133-139, 1995,

IDS #11) and as evidenced by Tamura et al (The Journal of Immunology 164:1432-41, 2000, IDS #13).

The claims are summarized as a humanized antibody that binds TAG-72 comprising CDRL1 and CDRL2 from LEN or all CDRs from CC49 and substitution of positions 60, 61, 62, 64 with the corresponding position in the 21/28"CL antibody and position 97 is a serine, a Fab fragment of the antibody, a composition comprising such, LCDR1 is SEQ ID NO:7 and LCDR2 is SEQ ID NO:8 and the humanized antibody has reduced immunogenicity compared to a parent antibody with CDRs from CC49 and a light chain of LEN and a heavy chain from 21/28'CL and a kit comprising the antibody.

Mezes et al teach a humanized antibody with CDRs from CC49 and a light chain FR of LEN and a heavy chain FR from 21/28'CL and the antibody binds TAG-72. Mezes et al does not teach an antibody with CDR1 and 2 of the light chain from LEN or substitutions of residues 60-62, 64 with those from the 21/28'CL antibody. These deficiencies are made up for in the teachings of Padlan et al.

Padlan et al teach humanization should preserve reactivity and eliminate immunogenicity and that there are a small amount of residues designated SDRs that are essential to antigen binding and Padlan teach Tables summarizing residues that may be important for antigen contact.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used residues identified in Padlan et al as important for antigen binding and replace the residues that are not important with human residues for reduced immunogenicity in the humanized antibody of Mezes et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used residues identified in Padlan et al as important for antigen binding and replace the residues that are not important with human residues for reduced immunogenicity in the humanized antibody of Mezes et al because Mezes et al teach a humanized CC49 antibody with frameworks of LEN and 21/28'CL which was chosen for their high degree of homology to CC49 light and heavy chains and in view of Padlan et al it would have been obvious to either substitute CDR1 and 2 of the light chain with the corresponding CDR in LEN because Padlan et al teach that for a kappa light chain (which LEN is) a 17 residue CDRL1 does not have any required residues for antigen binding and CDRL2 only has two residues at position 50 and 55 (see Table 2) which in LEN are the same as those in CC49 (as evidenced by Tamura et al only residue 53 is different between LEN and CC49) and thus it would be obvious to replace CDR1 and 2 in the light chain of CC49 with CDR1 and 2 in the light chain of LEN because this would obviously result in a less immunogenic antibody compared to the HUCC49 parent. In addition, it would have been obvious to use LEN residues because LEN was chosen to be most homologous to the CC49 light chain and substitution of LEN CDR1 and 2 in the light chain would result in less immunogenicity and Padlan et al teach that only SDRs should be retained (see page 133) and since there is. In addition it would have been obvious to substitute residues 60-62, and 64 of the CDRH2 in CC49 with those in the 21/28'CL antibody because Padlan et al teach these residues are also not important for antigen binding and can be replaced (see Table 5) and the 21/28'CL was the most homologous to the CC49 heavy chain as

taught by Mezes et al. In addition, it would have been obvious to have threonine at position 97 in the CDRH3 because this residue is found in the humanized parent antibody. Thus, replacing the claimed CDRs and residues would have been obvious to reduce immunogenicity as taught by Padlan et al.

Although claim 69 recites a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879